Effects of Exenatide on Diabetes Management and Weight Loss in a VA Population

Aeman Choudhury, PharmD, BCPS

One of the relatively new class of incretin mimetics, exenatide has not been as well studied as some other antidiabetic medications. This study aimed to evaluate how well the drug is working for veterans with type 2 diabetes and how closely VA providers are adhering to established guidelines for use.

Most practitioners would agree that a large proportion of their patients have suboptimally managed diabetes. Experts also agree that this disease is important to manage because of the multiple comorbidities associated with its progression. Although type 2 diabetes remains incurable, medical nutrition therapy, physical activity, weight management, self-management education, and pharmacologic interventions are all accepted components of an aggressive disease management srategy.[1] In particular, intensive blood glucose control to decrease microvascular complications has been emphasized in medical literature.

Various organizations have set strict glycemic targets to help clinicians gauge their patients' levels of diabetes control.[2] For instance, the American Diabetes Association (ADA) recommends that most patients work toward a hemoglobin A_{1c} (HbA_{1c}) level less than 7%, a fasting plasma glucose level between 70 and 130 mg/dL, and a two-hour postprandial glucose level less than 180 mg/dL.[3] The VA's guidelines regarding glycemic goals are parallel to those of the ADA.[4]

Dr. Choudhury is a clinical pharmacy specialist at the North Chicago VA Medical Center, North Chicago, IL.

Fortunately, a wide array of well studied medication options is available to help patients attain these goals. These treatment options have increased in recent years, with several new alternatives approved for use. Exenatide, which the FDA approved in 2005,[5] is one such agent. Although exenatide has been studied in the general type 2 diabetes patient population, to our knowledge, there have been no published studies on whether exenatide is helping VA patients reach their diabetes management goals. In addition, while the Pharmacy Benefits Management (PBM) Strategic Healthcare Group of the VA has determined specific criteria for exenatide use,[6] the extent to which these guidelines are being adhered to has yet to be determined.

To investigate these issues, a study of all patients taking exenatide at the North Chicago VA Medical Center (NCVAMC), North Chicago, IL was conducted. This article details the results of this study. Presented first, however, are facts about exenatide, the results of several studies conducted into exenatide's efficacy, and the PBM's specific criteria for exenatide use.

EXENATIDE

Exenatide is in the class of antidiabetes drugs known as incretin mimetics.[5] These drugs mimic the effects of the incretin hormones in the intestine that signal the body to make insulin. Exenatide mimics the natural incretin glucagon-like peptide-1 (GLP-1), which allows the drug to enhance glucose-dependent insulin secretion, restore first-phase insulin response, and suppress glucagon toward normal for a reduced glucose output. The drug additionally slows accelerated gastric emptying, which leads to decreased food intake and potential weight loss.

Exenatide is approved for use as monotherapy and as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who have not achieved adequate glycemic control and are taking metformin, a sulfonylurea, a thiazolidinedione (TZD), a combination of metformin and a sulfonylurea, or a combination of metformin and a TZD. The drug is administered through subcutaneous injection using a prefilled pen.[5]

It is important to note that cases of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, have been reported in patients treated with exenatide. It is recommended that patients with a history of pancreatitis be considered for other types of antidiabetes drugs.[5]

Most studies that analyze exenatide's ability to reduce HbA_{1c} levels include the use of metformin, a sulfonylurea, or a combination of the

two agents. One such study, which was funded by exenatide's manufacturer, focused on HbA_{1c} reduction and weight loss. During this 30-week, triple-blinded, placebo-controlled study, 336 participants with type 2 diabetes who had failed to achieve appropriate glycemic control with maximally effective metformin doses were randomly assigned to receive metformin plus either exenatide 5 µg, exenatide 10 µg, or placebo. The researchers found mean (SD) HbA_{1c} decreases of 0.78% (0.1%) in the exenatide 10 µg group and 0.4% (0.11%) in the exenatide 5 µg group ($P < .002$). Furthermore, it was noted that patients taking exenatide lost significantly more weight than those taking placebo ($P < .001$)—and that this weight loss was progressive and dose-dependent (mean [SD] weight loss of 2.8 [0.5] kg in the exenatide 10 µg group and 1.6 [0.4] kg in the exenatide 5 µg group).[7]

In another, similar study, researchers analyzed exenatide's effects when administered to a subgroup of patients with type 2 diabetes who had not achieved appropriate glycemic control with maximally effective sulfonylurea doses. During this triple-blinded, placebo-controlled study, 377 patients were randomly assigned to receive a sulfonylurea plus either exenatide or placebo. This study population was 60% male and had a mean (SD) age of 55 (11) years, a mean (SD) body mass index (BMI) of 33 (6) kg/m^2, and a mean (SD) HbA_{1c} level of 8.6% (1.2%). After 30 weeks of treatment, the mean (SD) HbA_{1c} changes from baseline were –0.86% (0.11%) in the exenatide 10 µg group, –0.46% (0.12%) in the exenatide 5 µg group, and 0.12% (0.09%) in the placebo group ($P < .001$). The results also showed a dose-dependent, progressive weight loss from baseline (mean [SD] loss of 1.6 [0.3] kg) in the patients treated with exenatide 10 µg.[8]

Kendall and colleagues analyzed the effects of adding exenatide to the regimen of patients with type 2 diabetes who already were taking metformin and a sulfonylurea. During this double-blinded, placebo-controlled study, 773 patients were randomly assigned to receive exenatide 5 µg, exenatide 10 µg, or placebo. While enrolled in the study, participants took their previous dose of metformin and were randomly assigned to receive either maximally effective or minimum recommended doses of a sulfonylurea. Patients had a mean (SD) age of 55 (10) years, a mean (SD) BMI of 33.6 (5.7) kg/m^2, and a mean (SD) baseline HbA_{1c} level of 8.5% (1%). The results of this study were similar to those seen with each of these agents utilized separately. After 30 weeks of treatment, HbA_{1c} was reduced by a mean (SD) of 0.8% (0.1%) with exenatide 10 µg and 0.6% (0.1%) with exenatide 5 µg. Patients treated with exenatide were more likely to achieve an HbA_{1c} level less than 7%—a goal reached by 34%, 27%, and 9% of patients treated with exenatide 10 µg, exenatide 5 µg, and placebo, respectively. Patients taking exenatide also showed a significant mean (SD) weight loss of 1.6 (0.2 kg) compared with patients taking placebo.[9]

EXENATIDE USE IN THE VA

In the VHA, exenatide utilization is strictly controlled through a nonformulary consultation review process managed by VA clinical pharmacists using criteria set forth by the PBM.[6] The VA stringently controls which patients begin therapy with exenatide, but it is left to the providers to follow up with the patients to determine the therapeutic success of the drug. The PBM criteria call for the initial exenatide prescription to be written for no more than two months, including refills, and for the prescribing clinician to reevaluate the patient within one to two months. Exenatide must be discontinued if there is less than a 10% decrease in HbA_{1c} after three to six months of therapy. The drug may be continued, however, if the patient has "reached glycemic target regardless of the magnitude of drop in HbA_{1c}."

Once a patient has been approved to use exenatide, he or she may continue to receive the drug until a provider discontinues the order or the order expires. It is important to determine whether the prescribing clinician is following up with the patient regarding glycemic targets and weight loss. Identifying percentages of patients who have met their glycemic goals, percentages of patients appropriately discontinued from exenatide, and the amount of patients' weight loss can help the VA to determine appropriate exenatide utilization and improve the management of veterans with type 2 diabetes.

STUDY METHODS

This study set out to determine the percentage of exenatide-treated patients who reached the HbA_{1c} goal level of less than 7%. Secondary objectives were: (1) to determine the percentage of patients who were appropriately discontinued from exenatide, as required by PBM criteria, after not reaching the HbA_{1c} goal and (2) to determine exenatide's effect on patients' weight loss.

The study was approved by the NCVAMC's Institutional Review Board and was designed as a retrospective chart review of all veteran patients at the facility who had been prescribed exenatide between June

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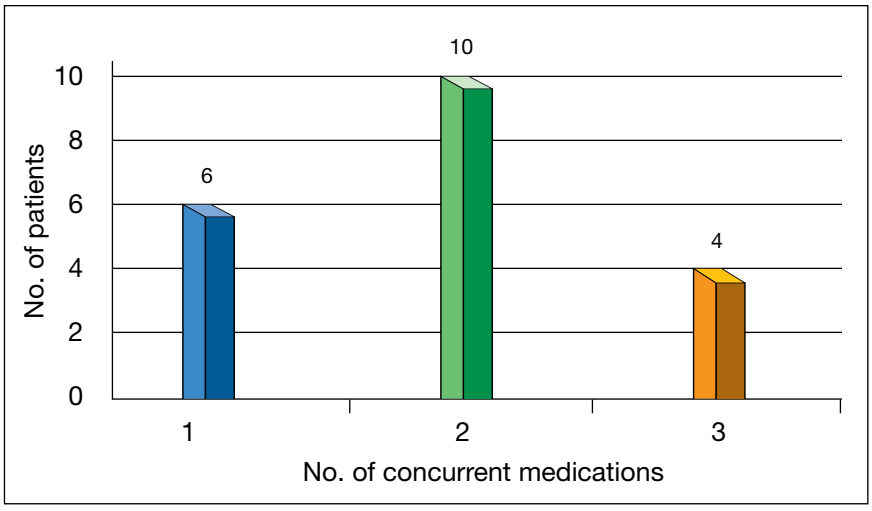

Figure 1. The number of concurrent diabetes medications the study patients were taking along with exenatide.

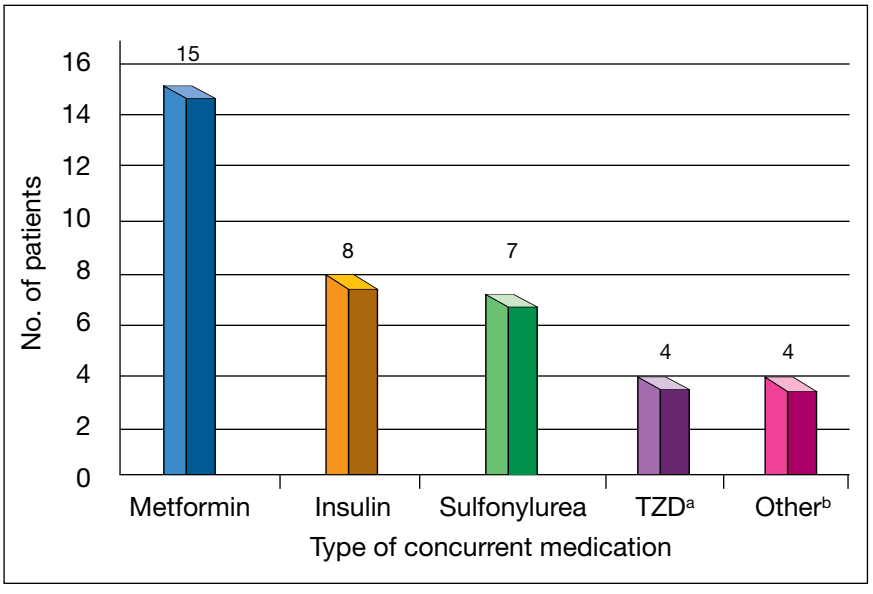

Figure 2. The type of concurrent medications taken with exenatide by the study patients. [a]TZDs = thiazolidinediones. [b]Other medications included: repaglinide (2), acarbose (1), and sitagliptin (1).

2005 and November 2007, regardless of their prescription's current status. There were no exclusion criteria. All patient-related data were obtained from the VA's computerized patient record system (CPRS).

CPRS was used to collect information on patients' age, gender, and race, as well as their weight and HbA_{1c} levels three months prior to initiation of exenatide therapy (baseline weight and HbA_{1c}). Data on how long patients were taking exenatide at doses of 5 µg and 10 µg were collected, and it was determined whether patients were evaluated by a health care provider within two months of active exenatide prescription. Data on patients' HbA_{1c} level and weight at three, six, nine, 12, 15, 18, 21, 24, 27, 30, and 33 months after initiation of exenatide were collected, when available. The name and dose of concurrent sulfonylurea, the dose of concurrent metformin, and the name and dose of any other concurrent diabetes management medication were collected. It was determined whether the patient took insulin at any time while taking exenatide or began taking any new diabetes management medications after exenatide had been initiated.

The Statistical Package for Social Sciences (SPSS) version 15.0 software (SPSS, Inc., Chicago, IL) was used to analyze all of the aforementioned data. All missing data were addressed by the last measurement carried forward method. Weight data were analyzed using paired *t* tests of the patients' baseline weight and the last available weight measurement while the patient was taking exenatide within the study period. In order to have a power of 0.9 and an alpha level of 0.05, the study sample for a paired *t* test must include at least 44 patients.

RESULTS

A total of 20 patients were prescribed exenatide at the NCVAMC during the study period. All patients were white men except one, who was a male Pacific Islander. The patients' mean (SD) age was 58.8 (6.3) years, their mean (SD) baseline weight was 127.8 (28.9) kg, and their mean (SD) last weight while taking exenatide was 121.1 (26.9) kg. All patients were taking one to three concurrent diabetes medications while taking exenatide (Figure 1). The most common of these medications were metformin, insulin, sulfonylureas, and TZDs

(Figure 2). The patients' mean baseline HbA_{1c} level was 9%.

At the end of the study period, 13 patients (65%) did not reach the HbA_{1c} goal of less than 7%, six (30%) did reach the goal, and one (5%) had no HbA_{1c} levels recorded during the study period (Figure 3). Eight patients (40%) should have been discontinued from exenatide according to PBM guidelines but continued taking the drug throughout the study, while six patients (30%) continued exenatide appropriately, five patients (25%) were discontinued from exenatide appropriately, and one patient (5%) had no information available on exenatide continuation (Figure 4). Of all the patients, 12 (60%) were appropriately reevaluated by a health care provider within two months of starting exenatide. During the course of treatment, 80% of patients lost weight (Figure 5). A paired samples *t* test showed this weight loss to be significant ($P = .002$; confidence interval, 2.86–10.6).

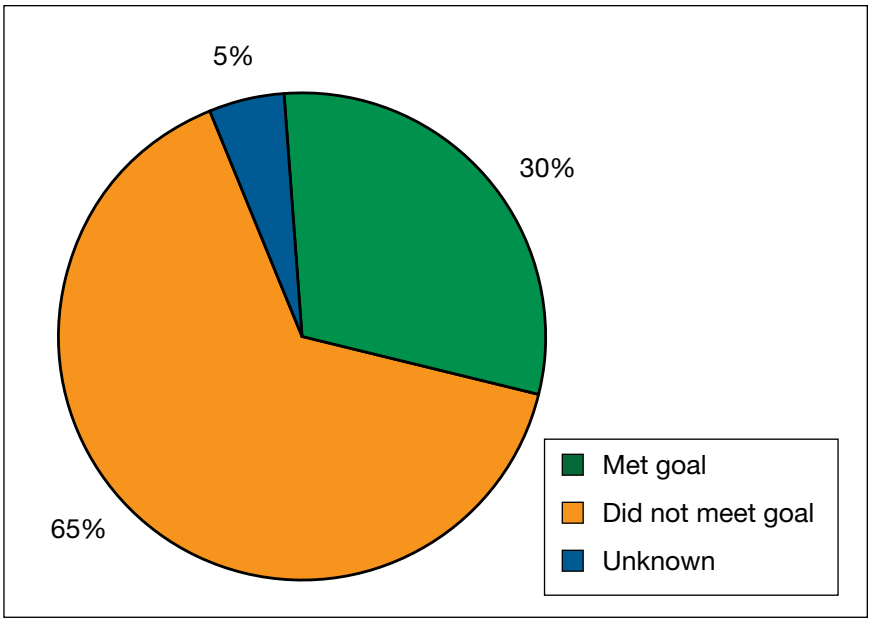

Figure 3. Percentage of study patients who reached the goal hemoglobin A_{1c} level of less than 7%.

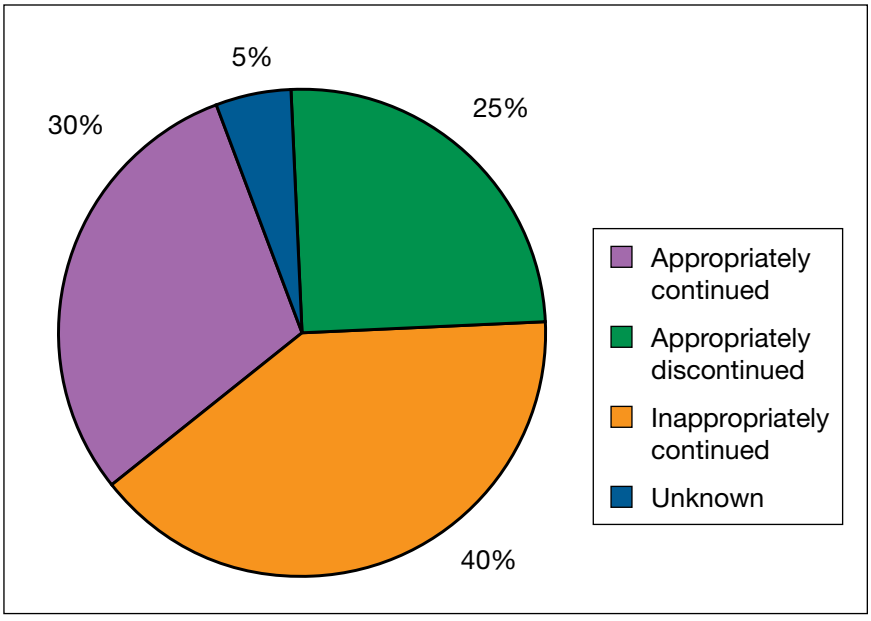

Figure 4. Percentage of study patients for whom exenatide was appropriately continued or discontinued according to VHA Pharmacy Benefits Management Strategic Healthcare Group guidelines.

DISCUSSION

The patient population of predominately white men included in this study reflects a typical VA medical center. At the time the study was conducted, exenatide was FDA-approved for use only in combination with metformin, a sulfonylurea, or a TZD. Thus, it is of note that eight patients were taking insulin and four were taking other non–FDA-approved combinations. To date, exenatide has not been approved for use with insulin. Since exenatide increases incretin mimetics and, thus, the release of insulin, however, some VA providers may believe that it is logical to use insulin and exenatide in combination. The VA nonformulary process also requires clinical pharmacists to evaluate the appropriateness of each initial request according to the PBM criteria.

These off-label combinations can be explained primarily by two common situations. First, a VA provider may request a nonformulary medication because the patient has been prescribed this medication by a provider

outside of the VA. If a patient has reached glycemic goals by the time a VA provider requests exenatide, this patient may receive the medication from the VA because it has been effective, even though it is not in line with FDA indications. Second, a VA provider may not be informed when a patient is prescribed a formulary diabetes medication after exenatide has been approved for use. In other words, some of the medications that patients were taking in addition to exenatide may have been ordered after exenatide was initiated.

Most patients in the study were seen within two months of exenatide initiation by a diabetes education nurse or the endocrine service for drug administration education and initial evaluation. The fact that only 60% of patients were evaluated within two months of therapy initiation may explain why eight patients—40% of all the study patients and 62% of those who did not reach the HbA_{1c} goal—were continued on exenatide inappropriately. No further statistics were conducted to validate this inference, however. It is worth noting that a medication change may not be documented in CPRS even though a patient has been verbally instructed to discontinue a medication. Also, many veterans receive care from non-VA providers and are lost to follow-up because they only come to the VA annually to refill their prescriptions.

During the study, 80% of the patients lost weight—although weight data were not available for one patient. A paired *t* test shows significant weight loss ($P = .002$) between baseline and the last weight measurement in the study period. Since only 20 patients were included in this study, however, statistical power was not attained. These findings reflect the significant weight loss observed in the medical literature discussed earlier.

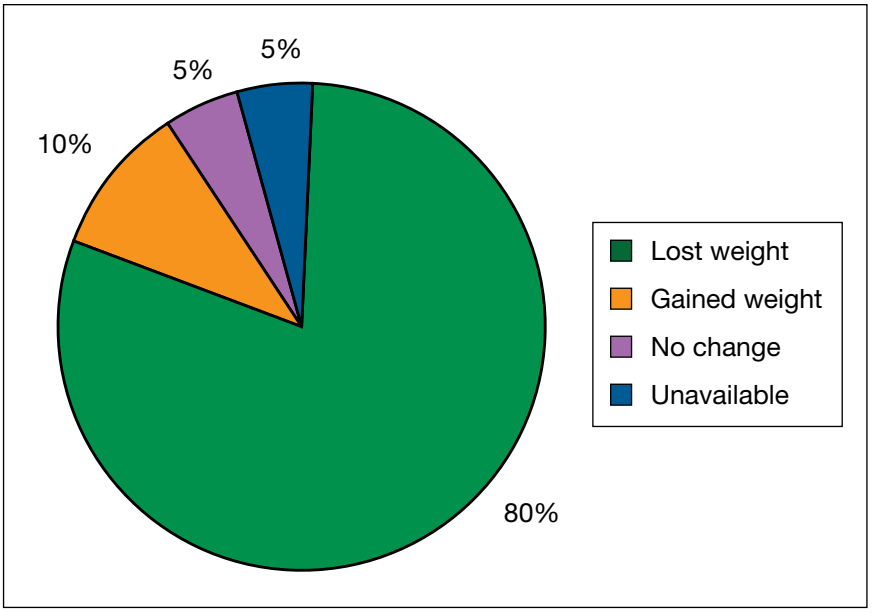

Figure 5. Study patients' weight changes while taking exenatide.

IN CONCLUSION

Overall, this chart review revealed that 30% of type 2 diabetic patients treated with exenatide at one VA medical center reached an HbA_{1c} level of less than 7%, which is similar to the rates reported in previously published studies.[7] The American Association of Clinical Endocrinologists guidelines project that, when utilized appropriately, the addition of exenatide to a patient's diabetes drug regimen may lower the HbA_{1c} level by 0.8% to 0.9%.[1] Since the mean HbA_{1c} level in this study was 9%, it was not expected that a majority of patients would reach their HbA_{1c} goals through the addition of exenatide.

The fact that only 30% of patients in this study reached their HbA_{1c} goals underscores how important it is for patients to receive appropriate follow-up and discontinuation from this drug if necessary. Restricting the maximum number of refills allowed for exenatide and permitting further renewals only after documentation of laboratory testing or clinic follow-up could potentially guarantee appropriate utilization of exenatide. Similar models of prescribing and dispensing are in place for the smoking cessation drug varenicline and the anemia drug darbepoetin at the NCVAMC. A cost analysis was not conducted as part of this study, however, and as exenatide has not gained the media attention that varenicline gained recently, enforcing such a policy may be difficult.

At least 80% of patients lost weight during the study period, and this outcome was determined to be significant. Further studies may evaluate the correlation between weight loss and HbA_{1c} reduction. Depending on the results of such studies, it may be appropriate to reserve future exenatide therapy for obese patients who require less than a 1% reduction in HbA_{1c}. ●

Acknowledgements

The author would like to thank Yinka Alaka, PharmD and Jennifer Javier, PharmD, BCPS for their help in writing the study protocol and Thomas

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Reutzel, PhD for his help with the study's statistical analysis.

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

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